CASE 4-20017D

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF
ULRICH POSANSKI
APPLICATION NO: 10/040,842
FILED: JANUARY 7, 2002
FOR: PHARMACEUTICAL COMPOSITIONS FOR SPARINGLY SOLUBLE THERAPEUTIC AGENTS

Art Unit: 1617
Examiner: Shengjun Wang

**MS: Appeal Brief**
Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

# APPEAL BRIEF

Sir:

This appeal is lodged in response to a Final Rejection dated September 23, 2003 finally rejecting claims 23-31. Applicants request reconsideration of the rejections and reversal of the Final Rejection.

1. Real Party In Interest:

The real party in interest is Novartis AG

2. Related Appeals and Interferences:

None.

3. Status of Claims:

Claims 23-31 are pending. Claims 23-31 (Appendix I) are under Final Rejection and are now on appeal.

4. Status of the Amendments:

The original claims and added claims 11-22 have been canceled. Claims 23-31 were added by amendment dated July 15, 2003. (it is noted that the Action dated September 23, 2003 incorrectly states that claim 22 is pending.)

5. Summary of the Invention:

The claims on appeal are directed to a pharmaceutical composition comprising a cyclosporin and a carrier which comprises:

a) about 10-50% by weight of a polyglycerol fatty acid ester co-surfactant;

b) about 5-40% by weight of a pharmaceutically acceptable oil comprising a triglyceride; and

c) about 10-50% by weight of a nonionic surfactant.

The claims are also directed to a process which comprises mixing components a), b), and c) and dispersing in said mixture the therapeutic agent.

6. Issues:

1. Whether the claims are obvious over the combination of three references: Akiyama (US'025); Hauer (US'625); and Reggio (US'169).

2.. Whether the claims are obvious over the combination of two references: Hauer (US'625) and Reggio (US'169).

7. Grouping of the Appealed Claims:

The claims on appeal may be grouped as follows: 1) claims 23-29; and 2) claims 30 and 31.

8. Arguments:

**1. Whether the claims are obvious over the combination of three references: Akiyama (US'025); Hauer (US'625); and Reggio (US'169).**

Claims 23-31 are rejected as obvious under 35 USC 103 over Akiyama (US'025) in view of Hauer (US'625), further in view of Reggio (US'169).

US '025 is directed to a solid (at room temperature) matrix, the function of which is to adhere to the gastrointestinal mucosa so as to prolong the residence there of the active ingredient. An essential element of the matrix is a "viscogenic agent", e.g., acrylic acid

polymers. US'025 does not concern itself with the problem of therapeutic agents which are sparingly soluble in water (e.g., the cyclosporins of the present invention). This can be seen from the broad range of agents listed at col. 6, lines 7-28 (none of which is structurally related to the cyclosporins). That the reference is not concerned with the problem of solubility is further demonstrated at col. 5, lines 53-54: "There is no particular limitation on the type of active ingredient." That the reference uses some components that are common in the pharmaceutical arts for a purpose different from that of the present invention is not the basis for an obviousness rejection.

US '625 is cited for its teaching that cyclosporins are known for their poor solubility and that various surfactants are known to be useful in cyclosporin formulations. However, this does not rectify the deficiency in the primary reference, as discussed above, since that reference does not address the issue of drug solubility. Further, there would be no motivation to combine these references since US '025 is directed to a solid which adheres to the gastrointestinal mucosa by incorporating as an essential element a viscogenic agent such as an acrylic acid polymer whereas the objective of US'625 is to provide a composition in the form of a microemulsion preconcentrate (see col. 5, lines 54-57). There is no teaching in US '025 that said viscogenic element may be removed. (No such viscogenic element is recited in the present claims.) Furthermore, the viscogenic agent must be positioned at or near the surface of the solid matrix (US '025, col. 9, lines 40-50.) A person of ordinary skill in the art would not consider combining a teaching whose purpose is to prepare a mucosa-adhering solid matrix composition which must contain at or near its surface a viscogenic agent with a teaching of a microemulsion preconcentrate. Lastly, US'625 teaches away from the present composition. The clinical trial described in US '625, col. 32, compares: 1) "Composition I" which comprises a hydrophilic component, a medium chain fatty acid triglyceride, and a hydrophilic surfactant, and 2) "Composition X", which comprises a hydrophilic component, an oil, and a lipophilic surfactant. The clinical trial shows improved bioavailability and reduced variability of Composition I over Composition X, thus teaching away from the presently claimed compositions which comprise a lipophilic surfactant as an essential ingredient.

The Examiner argues that it would be obvious to employ the presently claimed surfactants with a pharmaceutical agent such as a cyclosporin in the composition of US '025. Assuming *arguendo* that this were true, the result would be a mucosa-adhering solid matrix with a viscogenic agent at or near its surface - which is not the claimed invention.

The rejection is made further in view of Reggio (US'169). This reference concerns chewing gum, specifically a formulation with enhanced film-forming properties; i.e., a better bubble gum composition. Such a disclosure is totally irrelevant to one of ordinary skill in the art of preparing pharmaceutical formulations; i.e., the subject of the present invention.

Regarding the rejection of process claims 30 and 31 on the basis that merely mixing ingredients is *prima facie* obvious, this would only be true if the selection of the ingredients to be mixed is obvious and the result of said mixing is obvious. In the present case, for the reasons provided herein, there is nothing obvious about the selected compounds nor the desired results, i.e. cyclosporin-containing compositions with enhanced solubility, resorptive capacity, and bioavailability.

The Examiner responds that applicants cannot show non-obviousness by attacking the references individually. Applicants respectfully disagree. If a reference does not teach what the Examiner says it teaches; if a reference teaches away from what the Examiner says it teaches; or it statements in a reference can have a meaning different from the Examiner's stated meaning, then a reference can be attacked individually since the combination of references is invalid if any reference in the combination does not support the Examiner's conclusions.

Further, the Examiner responds that even if US '025 does not expressly state that surfactants are used to increase solubility, it suggests optimization. However, optimization is not an end it itself and provides no guidance to achieve any and all purposes. Clearly, many references actually teach or, at least, suggest optimization. However, to what end? In the case of US '025 the end would appear to be a better mucosa-adhering solid matrix with a viscogenic agent at or near its surface. The Examiner has not explained how such optimization is achieved by combining US '025 with the other two references, nor how such optimization to achieve the purpose of the US '025 reference would result in the presently claimed composition. Specifically, why would one of ordinary skill in the art remove the essential viscogenic agent from the surface of the solid matrix of US '025?

The Examiner also responds that US '169 is cited to show that polyglycerol esters are old surfactants. However, none of the specific components of the claimed composition is asserted to be novel. The invention is in the particular combination of components. The examiner states (Office Action dated January 15, 2003) that the selection "amongst equally suitable material" is obvious. However, the Examiner has not shown where the art teaches that the myriad of known polyglycerol fatty acid esters, triglyceride oils, and non-ionic surfactants are "equally suitable" materials. Nor has he shown that these specific esters, oils, and non-ionic surfactants in the claimed amounts are the ones to select from the even greater number of known pharmaceutically acceptable excipients.

There is no motivation in any of the documents for their combination with any reasonable expectation of achieving the desired results, i.e. cyclosporin-containing compositions with enhanced solubility, resorptive capacity, and bioavailability. It is deemed that the combination of these references does not make obvious the present invention.

**2. Whether the claims are obvious over the combination of two references: Hauer (US'625) and Reggio (US'169).**

Claims 23-31 are rejected under 35 USC 103 as obvious over Hauer (US'625), with an additional comment regarding Reggio (US'169). The rejection is traversed. The comments *supra* regarding Hauer and Reggio are incorporated herein. It is deemed that the combination of these references does not make obvious the present invention.

Regarding the rejection of the process claims on the basis that merely mixing ingredients is *prima facie* obvious, this would only be true if the selection of the ingredients to be mixed is obvious and results of said mixing is obvious. In the present case, for the reasons provided above, there is nothing obvious about the selected compounds nor the desired results, i.e. cyclosporin-containing compositions with enhanced solubility, resorptive capacity, and bioavailability.

There is no motivation in these documents for their combination with any reasonable expectation of achieving the desired results, i.e. cyclosporin-containing compositions with enhanced solubility, resorptive capacity, and bioavailability. It is deemed that the combination of these references does not make obvious the present invention.

It is believed that none of the claims are obvious under 35 USC 103. Accordingly, reconsideration of the propriety of the outstanding rejections under 35 U.S.C. 103 and allowance of the claims to issue as U.S. Letters Patent is respectfully solicited.

The Commissioner is hereby authorized to charge the fee under 37 CFR 1.17(c) of $**320**.00 to Deposit Account No. 19-0134

Respectfully submitted,

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Encls.: Appeal Brief in triplicate with Appendix
This page in duplicate
Date: January 21, 2004

## APPENDIX I

## CLAIMS ON APPEAL

23. A pharmaceutical composition comprising a solubilized therapeutic agent which is cyclosporin A or cyclosporin G and a carrier composition, said carrier composition comprising:

a) about 10-50% by weight, based on the carrier composition, of a polyglycerol fatty acid ester co-surfactant which is substantially pure or which is in the form of a mixture, having a hydrophilic-lipophilic balance of less than 10 (HLB value according to Griffin);

b) about 5-40% by weight, based on the carrier composition, of a pharmaceutically acceptable oil which is substantially pure or which is in the form of a mixture, comprising a triglyceride as essential lipophilic component; and

c) about 10-50% by weight, based on the carrier composition, of a nonionic surfactant which is substantially pure or which is in the form of a mixture, having an HLB value of more than 10;

and further optional pharmaceutically acceptable excipients.

24. A pharmaceutical composition of claim 23, comprising about 1-30% by weight, based on the total weight of the carrier composition, the therapeutic agent having a solubility in pure water of less than 500 mg/1000 mL.

25. A pharmaceutical composition of claim 23, wherein the therapeutic agent is cyclosporin A.

26. A pharmaceutical composition of claim 23, wherein the therapeutic agent is cyclosporin G.

27. A pharmaceutical composition of claim 23, wherein the polyglycerol chain contains up to and including 10 units of glycerol which are esterified with 1-10 acid esters of saturated or unsaturated carboxylic acids having an even number of 8-20 carbon atoms.

28. A pharmaceutical composition of claim 23, wherein component a) contains as polyglycerol fatty acid substantially pure polyglyceryl 2-tetrastearate, polyglyceryl 3-monooleate, polyglyceryl 3-stearate, polyglyceryl 6-dioleate, polyglyceryl 6-distearate, polyglyceryl 10-dioleate, polyglycerly 10-tetraoleate, polyglyceryl 10-decaoleate or polyglyceryl 10-decasterate, or a mixture of these compounds.

29. A pharmaceutical composition of claim 23, wherein

component b) contains as pharmaceutically acceptable oil ground nut oil, sesame oil, sunflower oil, olive oil, corn oil, soybean oil, castor oil, cottonseed oil, rapeseed oil, thistle oil, grapeseed oil, fish oil or neutral oil; and
component c) contains a nonionic surfactant with a hydrophilic component consisting of 15-60 units of ethylene oxide.

30. A process for the preparation of a pharmaceutical composition of claim 23, which comprises mixing components a), b), and c) and further optional pharmaceutically acceptable water-soluble excipients in any order, dispersing in this mixture the therapeutic agent and, if desired, processing the dispersion to a suitable dosage form for oral administration.

31. A process of claim 30, which comprises filling the dispersion into starch or hard or soft gelatin capsules.

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Respectfully submitted,

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b) about 5-40% by weight, based on the carrier composition, of a pharmaceutically acceptable oil which is substantially pure or which is in the form of a mixture, comprising a triglyceride as essential lipophilic component; and

c) about 10-50% by weight, based on the carrier composition, of a nonionic surfactant which is substantially pure or which is in the form of a mixture, having an HLB value of more than 10;

and further optional pharmaceutically acceptable excipients.

24. A pharmaceutical composition of claim 23, comprising about 1-30% by weight, based on the total weight of the carrier composition, the therapeutic agent having a solubility in pure water of less than 500 mg/1000 mL.

25. A pharmaceutical composition of claim 23, wherein the therapeutic agent is cyclosporin A.

26. A pharmaceutical composition of claim 23, wherein the therapeutic agent is cyclosporin G.

27. A pharmaceutical composition of claim 23, wherein the polyglycerol chain contains up to and including 10 units of glycerol which are esterified with 1-10 acid esters of saturated or unsaturated carboxylic acids having an even number of 8-20 carbon atoms.

28. A pharmaceutical composition of claim 23, wherein component a) contains as polyglycerol fatty acid substantially pure polyglyceryl 2-tetrastearate, polyglyceryl 3-monooleate, polyglyceryl 3-stearate, polyglyceryl 6-dioleate, polyglyceryl 6-distearate, polyglyceryl 10-dioleate, polyglycerly 10-tetraoleate, polyglyceryl 10-decaoleate or polyglyceryl 10-decasterate, or a mixture of these compounds.

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30. A process for the preparation of a pharmaceutical composition of claim 23, which comprises mixing components a), b), and c) and further optional pharmaceutically acceptable water-soluble excipients in any order, dispersing in this mixture the therapeutic agent and, if desired, processing the dispersion to a suitable dosage form for oral administration.

31. A process of claim 30, which comprises filling the dispersion into starch or hard or soft gelatin capsules.